Science at Sunrise, March 7, 2015

When should in vivo transporter-mediated drug-drug interaction studies be conducted?
A scientific perspective
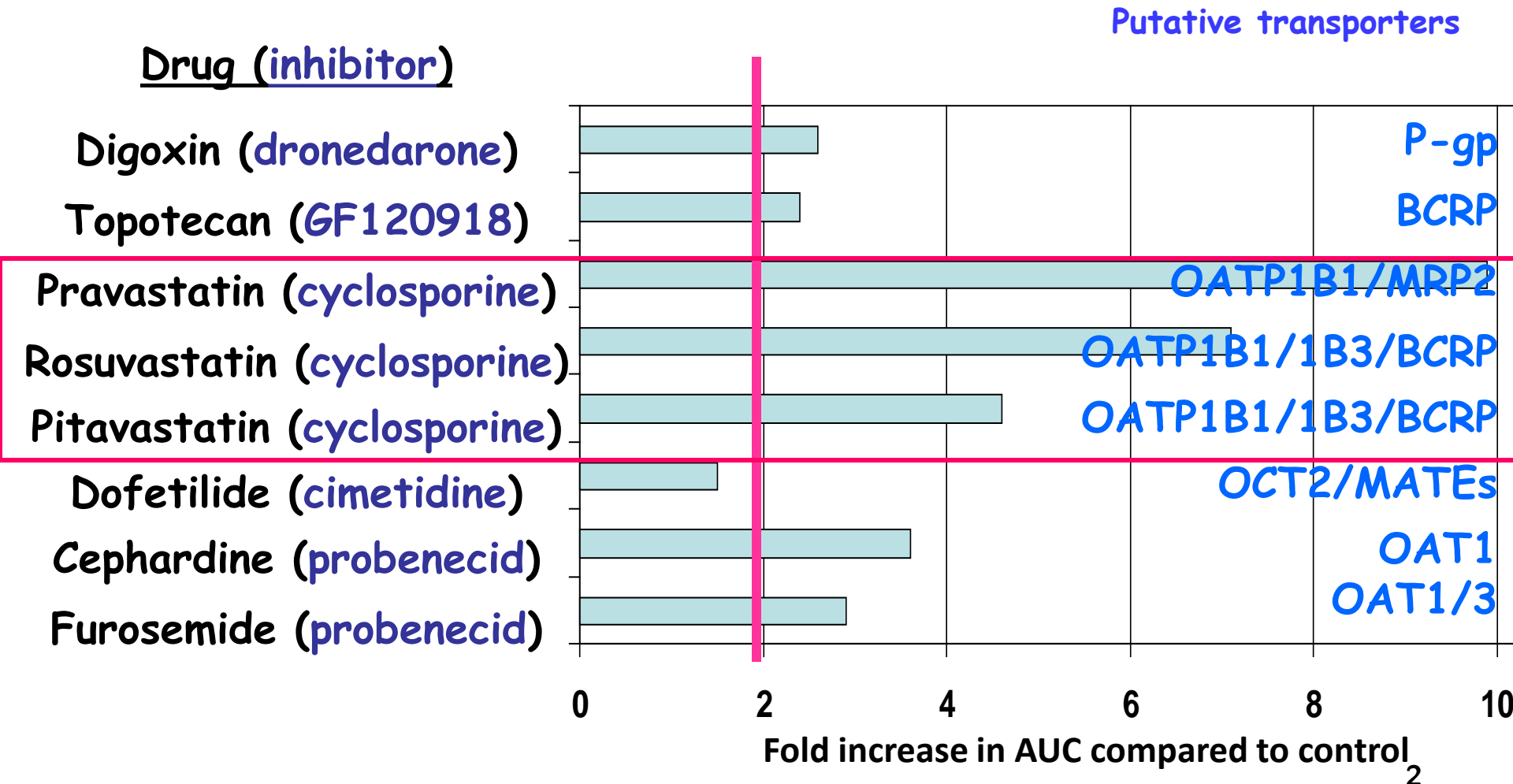
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Office of Clinical Pharmacology
Office of Translational Sciences
CDER, FDA

The views expressed in this presentation are those of the presenter and do not necessarily reflect the official policy of the FDA.

Why Evaluate Transporter-Based Drug Interactions?

Putative transporters

Drug (inhibitor)

Drug (inhibitor)	Fold increase	Putative transporter
Digoxin (dronedarone)	~2.5	P-gp
Topotecan (GF120918)	~2.4	BCRP
Pravastatin (cyclosporine)	~10	OATP1B1/MRP2
Rosuvastatin (cyclosporine)	~7	OATP1B1/1B3/BCRP
Pitavastatin (cyclosporine)	~4.6	OATP1B1/1B3/BCRP
Dofetilide (cimetidine)	~1.5	OCT2/MATEs
Cephardine (probenecid)	~3.6	OAT1
Furosemide (probenecid)	~2.9	OAT1/3

Fold increase in AUC compared to control

0   2   4   6   8   10

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Regulatory Guidance/Guideline on Drug Interactions

- U.S. Food and Drug Administration (FDA)'s Draft Guidance for Industry: Drug Interaction Studies—Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations (2012)

    (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf)

    –In addition to P-gp, transporter-related drug interaction evaluations and decision trees are included for additional transporters (BCRP, OATP1B1/3, OAT1/3 and OCT2)

- European Medicines Agency (EMA) Guideline on the Investigation of Drug Interactions (2012)

    (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129606.pdf)

- Pharmaceuticals Medical Devices Agency (PMDA) Draft Guideline on Drug Interactions (2013)

    (http://search.e-gov.go.jp/servlet/Public?CLASSNAME=PCMMSTDETAIL&id=495130206)

Which transporters are clinically important and should be considered for evaluation during drug development?

- Drug-Drug Interactions (DDI)

- Beyond DDI (e.g., toxicity, efficacy)

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Clinical Pharmacology & Therapeutics

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Published for the American Society for Clinical Pharmacology and Therapeutics by Nature Publishing Group

HUMAN DRUG TRANSPORTERS
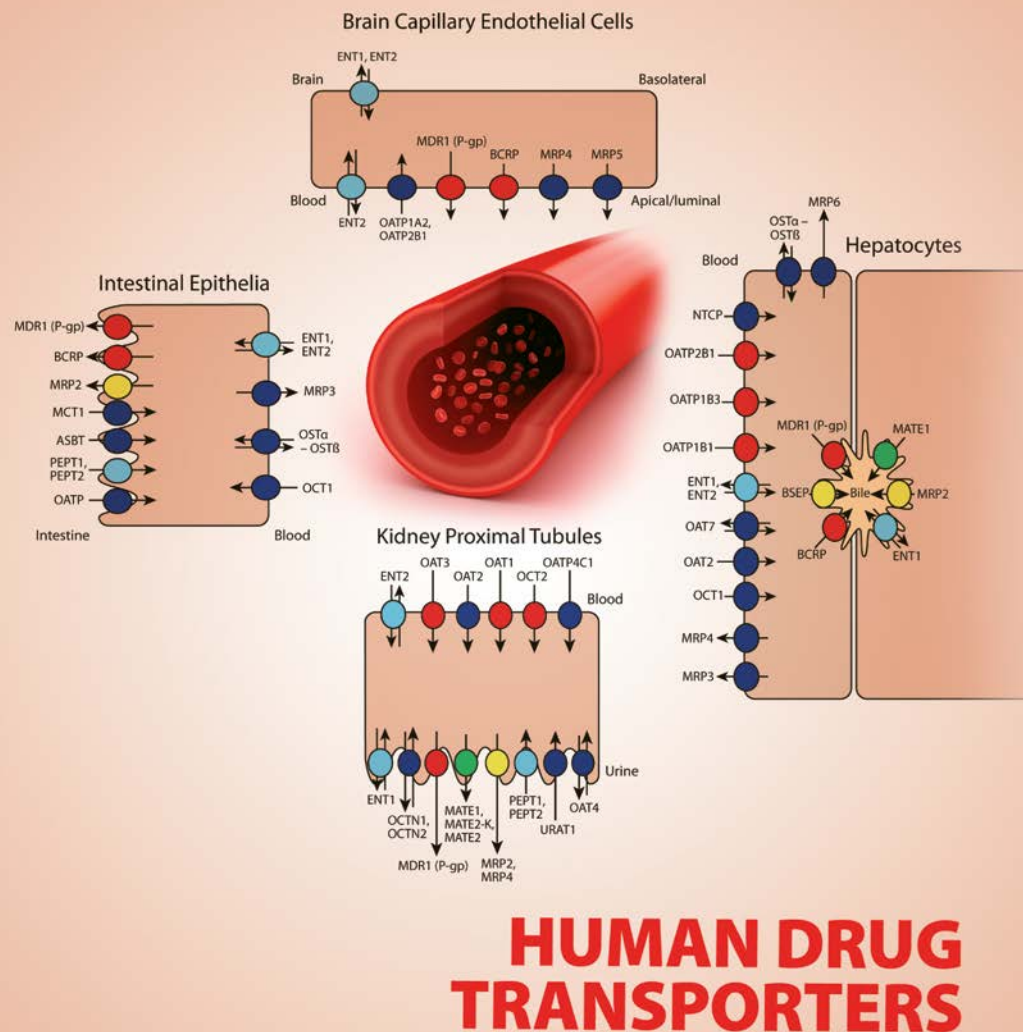
7 whitepapers/commentaries have been published in July 2013 issue of Clinical Pharmacology and Therapeutics (CPT):

- Emerging transporters of clinical importance: multidrug and toxin extrusion protein (MATEs), multidrug-resistance protein 2 (MRP2), bile salt export pump (BSEP)
- Transport *in vitro–in vivo* extrapolation/PK best practices
- Transporter pharmacogenomics
- CNS distribution: no to low risk of clinical drug interactions
- Transport *in vitro* methods: best practices
- Intracellular concentrations in efflux interactions
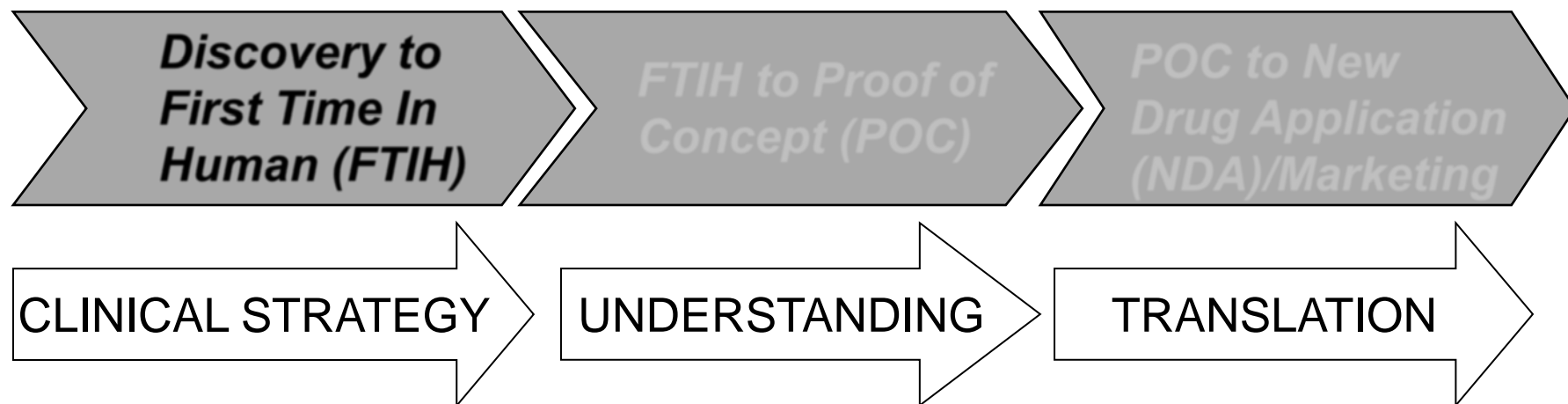- Transporters in drug development: regulatory and industrial perspectives

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The Challenges to Study Transporter DDI

- The issues presented by transporters are significantly more complex than for metabolizing enzymes
    - Involved in absorption, distribution and excretion: multiple processes of concern
    - Broad tissue distribution: different effects at different sites
    - Functional redundancy: different transporters and different subfamilies
    - Uptake and efflux transporters: need to consider both to assess the overall effect
    - Applicability of kinetic parameters and their interpretation
    - Measuring drug exposure in plasma may not reflect impact on a drug's disposition (e.g., toxicity)

Approaches

- Understand the clinical question
- Assess NME as a substrate or inhibitor of various enzymes and transporters to understand its DDI potential
  - An integrated approach (in vitro, in vivo, in silico)
    - Decision models
      - Consider all mechanisms to understand clearance pathways and describe variability and/or DDI
      - Basic → Mechanistic (static or PBPK)
  - Follow up studies
- Translate results into labeling

Drug Transporter Assessment Strategy

Discovery to First Time In Human (FTIH)	FTIH to Proof of Concept (POC)	POC to New Drug Application (NDA)/Marketing
CLINICAL STRATEGY	**UNDERSTANDING**	**TRANSLATION**

CLINICAL STRATEGY
- Therapeutic area
  - Comedicines
- Product Profile
- Development Plan
- Physicochemical properties

UNDERSTANDING
- Non-clinical studies (in vitro and in vivo)
- Clinical Studies
  - Pharmacokinetics
  - Safety

TRANSLATION
- Drug labeling
- Non-clinical mechanistic and/or investigative studies
- Clinical Studies

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Evaluation of NME as a <u>Substrate</u> for Transporters

Does the drug level depend on a given transporter?

Other trasnporters, e.g., MRP, may need to be evaluated.

All NMEs

Hepatic or biliary secretion major? e.g., ≥ 25% total clearance?

Renal active secretion major? e.g., ≥ 25% total clearance?

Yes or unknown

Yes or unknown

Determine whether NME is a <u>P-gp and/or BCRP</u> substrate in vitro

Determine whether NME is an <u>OATP1B1 or OATP1B3</u> Substrate in vitro

Determine whether NME is an <u>OAT1, OAT3 or OCT2</u> substrate in vitro

Also consider MATEs

Refer to P-gp and BCRP decision tree for the need to conduct *in vivo* studies

Refer to OATP1B1/1B3 decision tree for the need to conduct *in vivo* studies

Refer to OAT1/3 and OCT2/MATE decision tree for the need to conduct *in vivo* studies
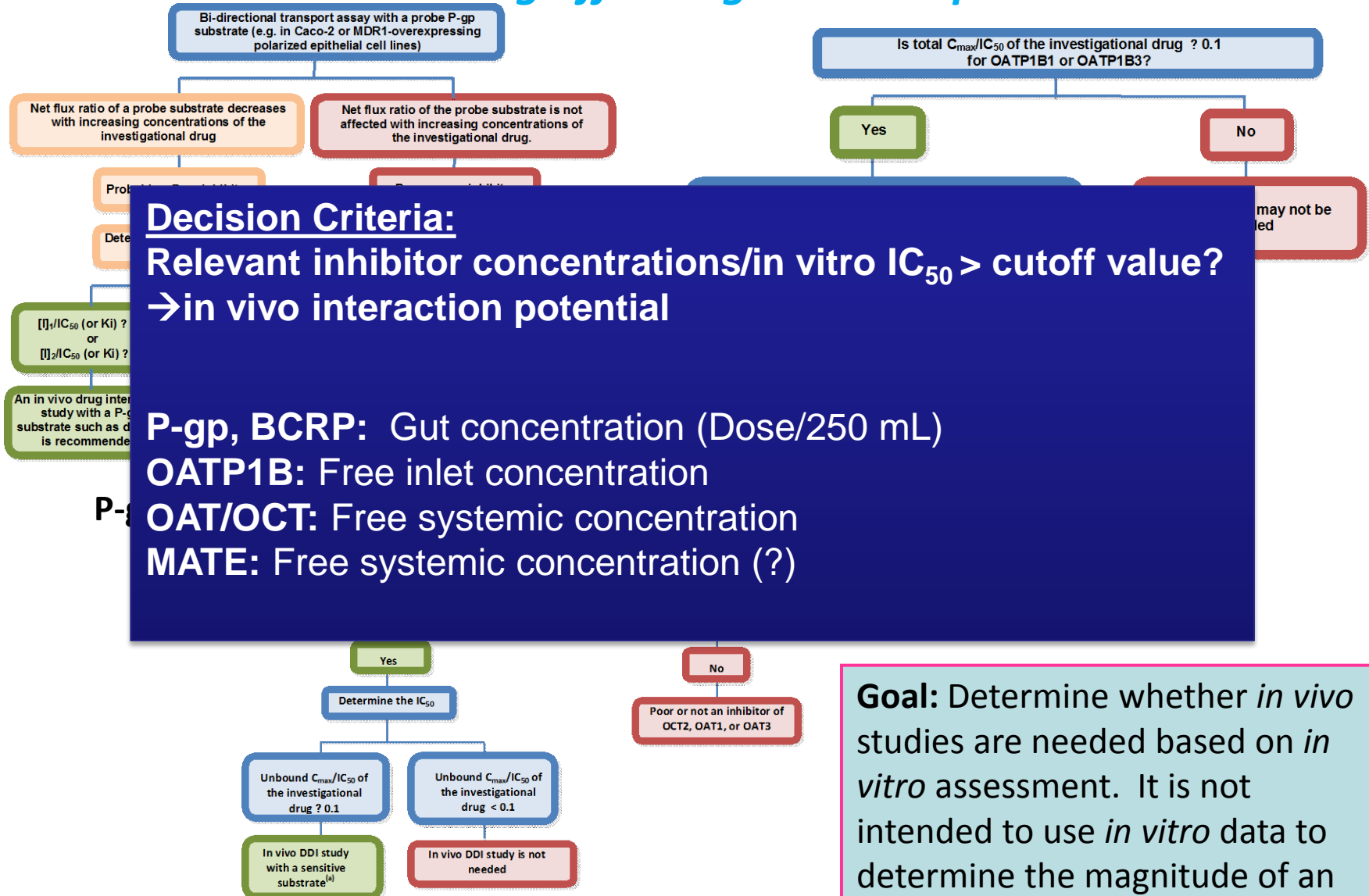
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NME as a Substrate
Does the drug level depend on a given transporter?

- Route of elimination
  - Hepatic major
  - Renal major
  - Rate limiting step
- Physicochemical properties of the drug
  - e.g., BCS or BDDCS
- Structure
  - e.g., OATs for anions and OCTs for cations
  - Caveat: some cations transported by OATs (cimetidine, sitagliptin)
  - Similarity to known substrates
- In vitro assays → A mechanistic understanding of the clearance of the drug
  - Sources of variability and potential for DDI
- Other factors to consider for DDI studies:
  - Safety margins, therapeutic range, co-mediations that are known transporter inhibitors in the indicated patient populations, is there known polymorphism of the transport pathway?

Evaluation of NME as an __Inhibitor__ for Transporters

Does the drug affect a given transporter?

Bi-directional transport assay with a probe P-gp substrate (e.g. in Caco-2 or MDR1-overexpressing polarized epithelial cell lines)

Is total C_{max}/IC_{50} of the investigational drug ≥ 0.1 for OATP1B1 or OATP1B3?

Net flux ratio of a probe substrate decreases with increasing concentrations of the investigational drug

Net flux ratio of the probe substrate is not affected with increasing concentrations of the investigational drug.

Yes

No

...may not be ...led

$[I]_1/IC_{50}$ (or Ki) ?
or
$[I]_2/IC_{50}$ (or Ki) ?

An in vivo drug inter... study with a P-g... substrate such as d... is recommende...

Decision Criteria:

Relevant inhibitor concentrations/in vitro IC_{50} > cutoff value?

→in vivo interaction potential

P-gp, BCRP: Gut concentration (Dose/250 mL)

OATP1B: Free inlet concentration

OAT/OCT: Free systemic concentration

MATE: Free systemic concentration (?)

P-g...

Yes

Determine the IC_{50}

No

Poor or not an inhibitor of OCT2, OAT1, or OAT3

Unbound C_{max}/IC_{50} of the investigational drug ≥ 0.1

Unbound C_{max}/IC_{50} of the investigational drug < 0.1

In vivo DDI study with a sensitive substrate[a]

In vivo DDI study is not needed

OAT1/OAT3/OCT2/MATEs

Goal: Determine whether *in vivo* studies are needed based on *in vitro* assessment. It is not intended to use *in vitro* data to determine the magnitude of an *in vivo* interaction.

NME as an Inhibitor
Does the drug affect a given transporter?

- Inhibitors can be substrates or non-substrates for a given transporter.

- The need to study DDI depends on whether drugs are likely co-administered with known substrates of major human transporters.

- Other factors to consider: indications, and whether the NME may affect other pathways.

In Vitro Methodologies

- *In vitro* assessments are critical to help determine the clearance mechanism and DDI potential.
- "Best Practice" of *in vitro* assay methodology is needed to ensure quality of *in vitro* assessments (e.g., reliable, reproducible and validated).
- The sources of the variability need to be understood, e.g.,
  - Different laboratories
  - Different in vitro cell systems
  - Different substrate/inhibitor
- The processes need to be standardized in each laboratory.
  - Each laboratory may develop criteria internally with known positive and negative controls ("calibration")

Need best practices and standardized approaches

Translating *In Vitro* Transporter Data into Clinical Predictions: What We Know and Where We Are Going

CHAIRS

Yong Huang, PhD, Optivia Biotechnology Inc.

Xin-Ning Yang, PhD, US Food and Drug Administration

In Vitro Models and Methodologies for Evaluating Drug Transport: Advantages, Limitations and Current Challenges
Harma Ellens, PhD, GlaxoSmithKline

Putting it All Together: Transporter Function in the Context of Organ Systems
Adrian S. Ray, PhD, Gilead Sciences Inc.

Translating In Vitro Transporter Studies into In Vivo Predictions: Successes, Challenges and Future Directions
Leslie Benet, PhD, University of California, San Francisco

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Challenges and Gaps between In Vitro and In Vivo
--Basic Models

P-gp (using $[I]_1$ or $[I]_2/IC_{50}$)
Etravirine or Maraviroc / Digoxin: False positive
$\rightarrow$Concomitant induction?
Talinolol / Digoxin: False negative prediction

OATP1B (using Free $[I]_{inlet}/IC_{50}$, R)
Gemfibrozil / Pitavastatin: False negative
-> Gemfibrozil glucuronide also inhibits OATP1B

Teriflunomide / Rosuvastatin: False negative
 if only consider OATP1B.
 -> BCRP inhibition also involved.

OCT2 (using Free C_{max}/IC_{50})
Dolutegravir / Metformin: False negative
using one IC_{50} reported (~20 fold difference from
two sources) $\rightarrow$ non-specific binding?

Considerations:
- Substrate dependent inhibition
- Uncertainty about intracellular
   concentrations
- Non-specific binding
- Multiple processes
  (absorption/distribution/
   excretion)
- Multiple transporters involved
- Transporters-Enzymes
   Interplay
- Metabolite as inhibitor
- Mechanistic discrepancy
      …….

Zhang L, et al. Xenobiotica (2008); Agarwal S, et al. J Clin Pharmacol (2013)
Lepist EI, et al. Kidney Int. (2014; Zong J, et al. J Int AIDS Soc.(2014); TIVICAY Prescribing Information
Sharma P, et al. Eur J Pharm Sci (2012); AUBAGIO Prescribing Information; NDA 202992 Review (Drugs@FDA)

Creatinine-Drug Interactions

- Creatinine is found to be a substrate of multiple renal transporters including OCT2, MATE1, MATE2K, and OAT2.

- An increase in serum creatinine can be due to 1) renal toxicity or 2) inhibition of creatinine transport pathways by new molecular entities.
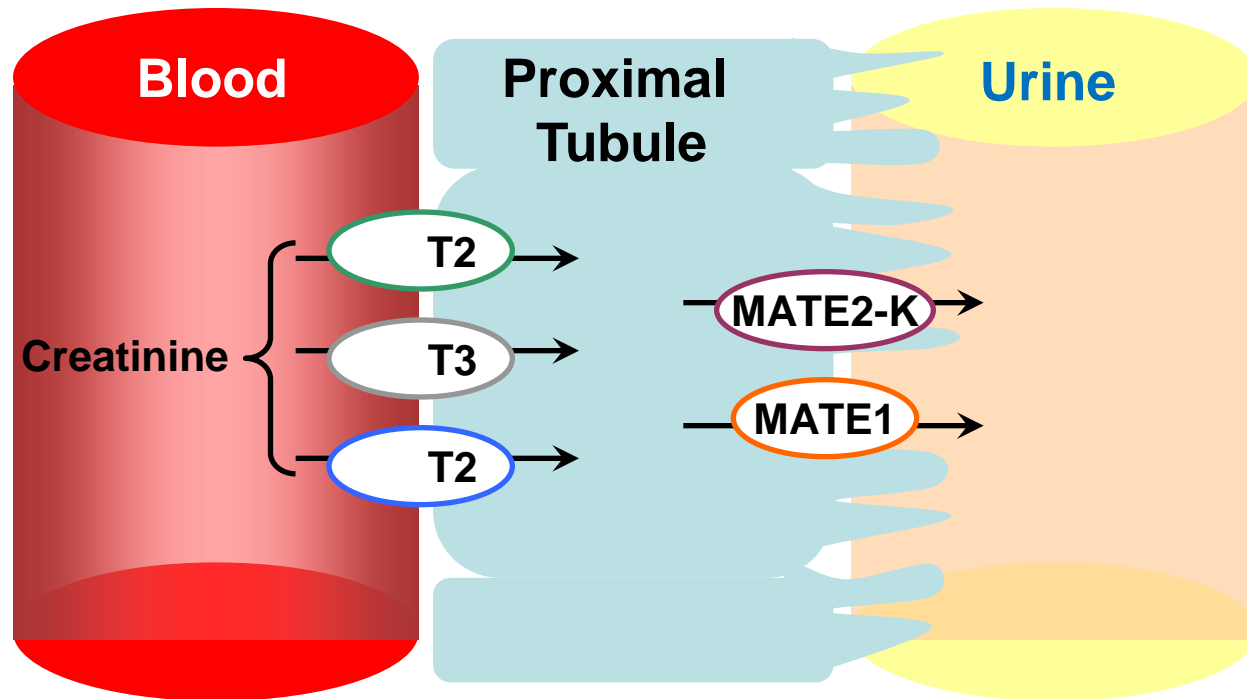

Figure: Lepist E-I, et al., Kidney Int. 2014, 86(2):350-7.

Inhibition of renal transporters may account for the increase in serum creatinine

Drug Name	IC$_{50}$ or Ki (μM)			FREE Cmax / IC$_{50}$ or Ki			TOTAL Cmax / IC$_{50}$ or Ki		
	OCT2	MATE1	MATE2-K	OCT2	MATE1	MATE2-K	OCT2	MATE1	MATE2-K
AZD0837 *	0.7	0.28	n.d.	0.21	0.53	n.d.	1.1	2.9	n.d.
Cimetidine	120	2.5	4.5	0.08	3.9	2.1	0.10	4.8	2.7
Cobicistat	8.2	1.9	34	0.007	0.03	0.002	0.27	1.2	0.07
Dolutegravir	0.07	4.7	> 300	1.87	0.03	<0.001	187	2.8	< 0.04
DX-619	0.94	0.82	0.1	7.7	8.8	72	24	28	229
GSK-1	23	3.4	11	0.07	0.49	0.15	0.33	2.2	0.7
Pyrimethamine	10 ± 2	0.093 ± 0.011	0.059 ± 0.008	0.03	3.2	5.0	0.23	25	39
Trimethoprim	60 ± 19	6.2	1.4	0.13	1.3	5.8	0.24	2.3	10.4

Common features:

Rapid onset, transient increase, no changes in aGFR or other renal biomarkers, show inhibition of renal transporters.

Can increase in creatinine concentration be used as an "indicator" of in vivo renal transporter inhibition by the new molecular entity?

Can interactions with creatinine predict DDI with metformin or other renal transporter substrates?

V Arya, X Yang, et. al., ASCPT 2014, Atlanta, GA.

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Dolutegravir (HIV)

Adverse Reactions

•Dolutegravir has been shown to ↑ sCr due to inhibition of tubular secretion of creatinine without affecting renal glomerular function.

Drug Interactions

•In vitro, dolutegravir inhibits OCT2 (1.9 uM) and MATE1 (6.3 uM).

•In vivo, dolutegravir inhibits tubular secretion of creatinine by inhibiting OCT2 and potentially MATE1.

•Dolutegravir may increase plasma concentrations of drugs eliminated via OCT2 or MATE1 (dofetilide and metformin).

Abstract (HIV Drug Therapy Glasgow Congress 2014):

The effect of dolutegravir on the pharmacokinetics of metformin in healthy subjects
Jian Zong, Julie Borland, Fred Jerva, Brian Wynne, Mike Choukour, Ivy Song

"Plasma exposures of metformin were significantly increased when co-administered with DTG". Metformin AUC ↑by 66% or 111% (depending on doses of dolutegravir). PD? (determined by the clearance of probe drug, para-amino hippurate) compared with the placebo.

http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/204790s001lbl.pdf

Transporters in tissue-specific drug distribution that may not be correlated with systemic exposure
--Metformin PK and PD were not correlated

PHARMACOKINETICS AND DISPOSITION

N^1-methylnicotinamide as an endogenous probe for drug interactions by renal cation transporters on the metformin–trimethoprim interaction

Fabian Müller · Constanza A. Pontones · Bertold Renner ·
Maren Mieth · Eva Hoier · Daniel Auge · Renke Maas ·
Oliver Zolk · Martin F. Fromm

PT-14   ASCPT 2015 Abstract

PYRIMETHAMINE, A MATE TRANSPORTER INHIBITOR, INCREASES THE SYSTEMIC EXPOSURE TO METFORMIN BUT DOES NOT INCREASE ITS BLOOD GLUCOSE LOWERING ACTION.

J. Oh,[1] S. Yi,[1] A. Kim,[1] S. Lee,[1] J. Cho,[1] S. Yoon,[1] I. Jang,[1] J. Chung[2]; [1]Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital, Seoul, Korea, Republic of, [2]Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Bundang Hospital, Seongnam, Korea, Republic of.

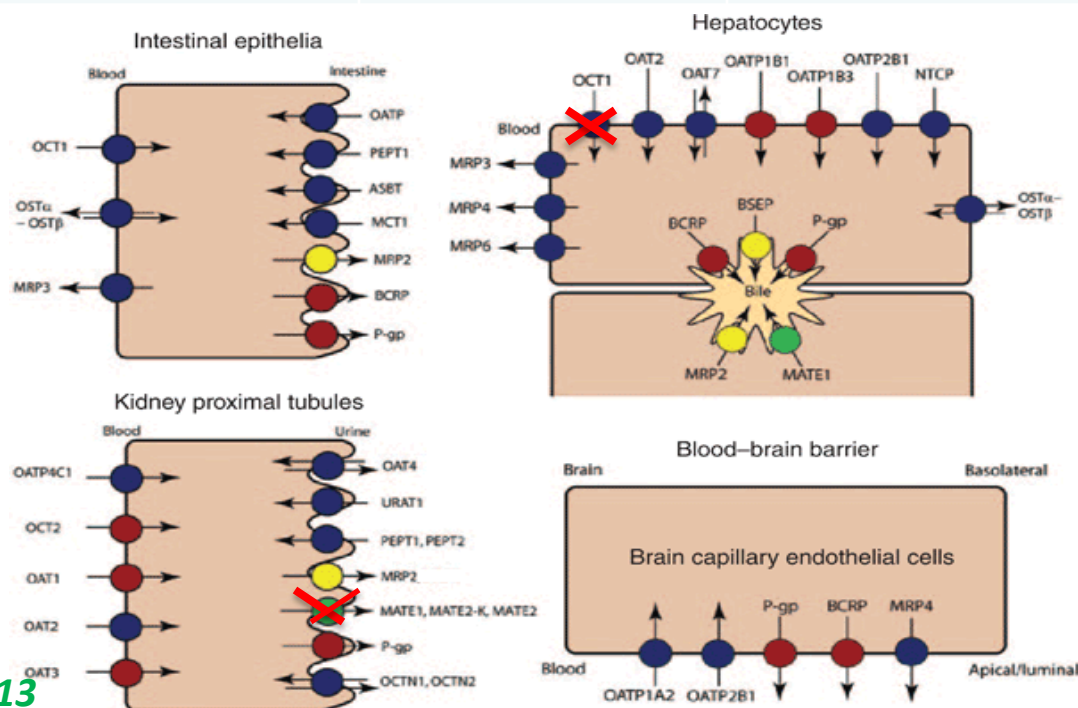|	PK	Possible Mechanism?	PD	Possible Mechanism?
Trimethoprim	↑ Systemic exposure ↓ Renal CL	Inhibition of MATE-1, MATE-2K in the kidney	↓ Glucose lowering effect	Inhibition of OCT1 in the liver
Pyrimethamine	↑ Systemic exposure ↓ Renal CL	Inhibition of MATE-1, MATE-2K in the kidney	↓ Glucose lowering effect	Inhibition of OCT1 in the liver

Figure:
Hillgren, et al.
Clin Pharmacol Ther, 2013

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NMN (N1-methylnicotinamide), Another Potential Marker for Renal Transporters?

- In vitro studies revealed that NMN is a substrate of OCT2, MATE1, and MATE2-K with comparable Km values around 350 μM.

- Correlate with metformin?
  - "The magnitude of trimethoprim-induced CL_R reductions positively correlated between NMN and metformin (r_S=0.727, p=0.010)"

- Pronounced diurnal changes in NMN plasma concentrations at the baseline

- Ethnicity difference
  - E.g., C_{max} was considerably higher in the Caucasian subjects (40 ng/ml) compared to the Japanese individuals (~18 ng/ml)

Ito S, et. al., Clin Pharmacol Ther 92:635–641, 2014;
Müller F, et. al., Eur JCP, 71:85–94, 2015

Need More Mechanistic Models

- Transporters are important for tissue distribution.
- The consequence of the interaction mediated by transporters may not always be apparent if an in vivo human DDI study only measures systemic exposure.
  - PK may not change in the same direction as PD
- Determining whether the NME is a substrate or inhibitor of key transporters can help to build mechanistic models to understand the underlying clinical consequences, such as increased toxicity signal or altered efficacy markers due to altered tissue distribution of a substrate drug.
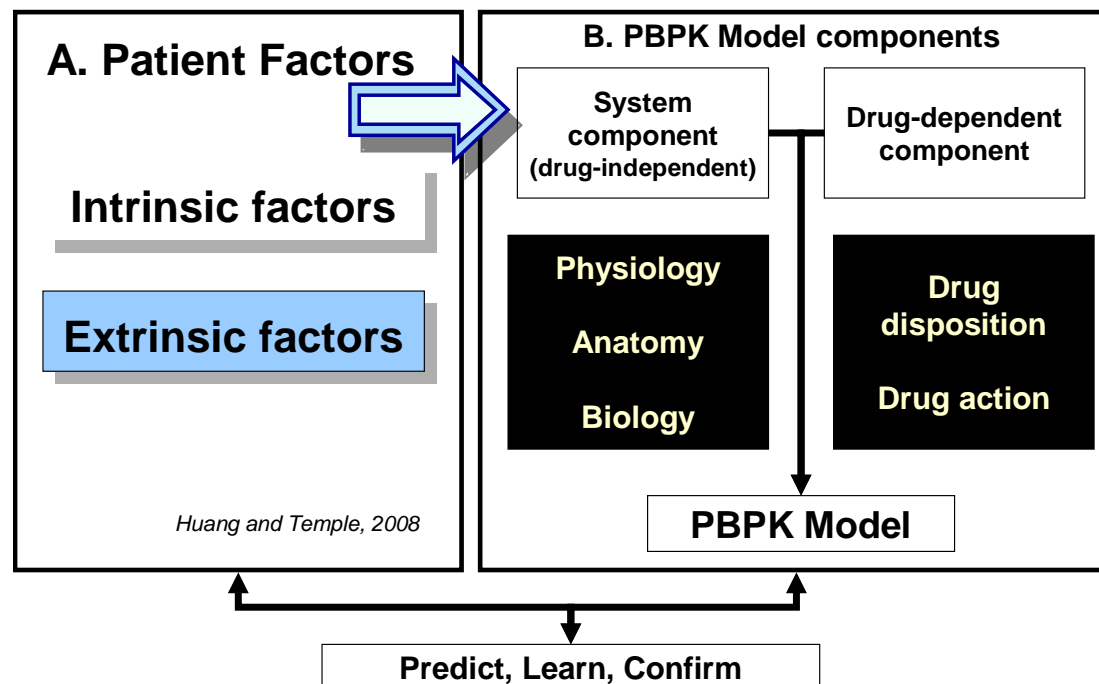
A. Patient Factors

Intrinsic factors

Extrinsic factors

Huang and Temple, 2008

B. PBPK Model components

System component (drug-independent)

Drug-dependent component

Physiology

Anatomy

Biology

Drug disposition

Drug action

PBPK Model

Predict, Learn, Confirm

Figure: Adapted from Zhao P, et al Clin Pharmacol Ther 2011

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Mechanistic Pharmacokinetic Modeling for the Prediction of Transporter-Mediated Disposition in Humans from Sandwich Culture Human Hepatocyte Data

Hannah M. Jor
Sonya C

ORIGINAL RESEARCH ARTICLE

Towards Quantitation of the Effects of Renal Impairment and Probenecid Inhibition on Kidney Uptake and Efflux Transporters, Using Physiologically Based Pharmacokinetic M

Vic
Jen
Kat

Prediction of Renal Transporter Mediated Drug-Drug Interactions for Pemetrexed Using Physiologically Based Pharmacokinetic Modeling

Maria M. Posada, James A. Bacon, Karen B. Schneck, Rommel G. Tirona, Richard B. Kim,
llgren

Physiologically Based Pharmacokinetic Modeling in Drug I Pharma

HM Jones[1], Y Ch
M Zheng[9] and SD

CPT, March 2015

Table 1 Confidence, limitations, and challenges for different PBPK applications

Application		Level of confidence	Limitations and challenges
Preclinical and clinical PK prediction	CYP cleared substrates	Moderate to high	No significant limitations or challenges for liver metabolism from *in vitro* systems for BCS I and II drugs. Intestinal metabolism is more challenging.
	Non-CYP metabolically cleared substrates	Low to moderate	Hepatocytes predictive for glucuronidation and some other non-P450 processes. Expression patterns and scaling factors for many non-CYP enzymes poorly defined.
	Clearance/absorption by active transport	Low	Transporter abundances and activity scaling factors poorly understood.
	Elimination by combination of metabolism and transport	Low	Interplay of multiple transporters and metabolic enzymes very challenging.

PBPK model to understand PK and DDI (Simeprevir, approved 2013, HCV)

- ✓ Saturable active uptake in hepatocyte

- ✓ Liver:blood ratio is 29:1 in rats

- ✓ In humans, 91% of the oral dose was recovered in feces with parent drug accounting for 31% of the dose, suggesting hepatic uptake and following metabolism and/or biliary excretion

- → Significant hepatic uptake

Questions addressed by the submitted PBPK modeling report and additional information requested by OCP include:

1. What are the major mechanisms contributing to non- linear pharmacokinetics of simeprevir?

2. Can drug-drug interaction with simeprevir be predicted?

In addition, sponsor simulated PK of simeprevir in various specific populations and projected liver concentrations of simeprevir in Caucasian and Asian HCV subjects.
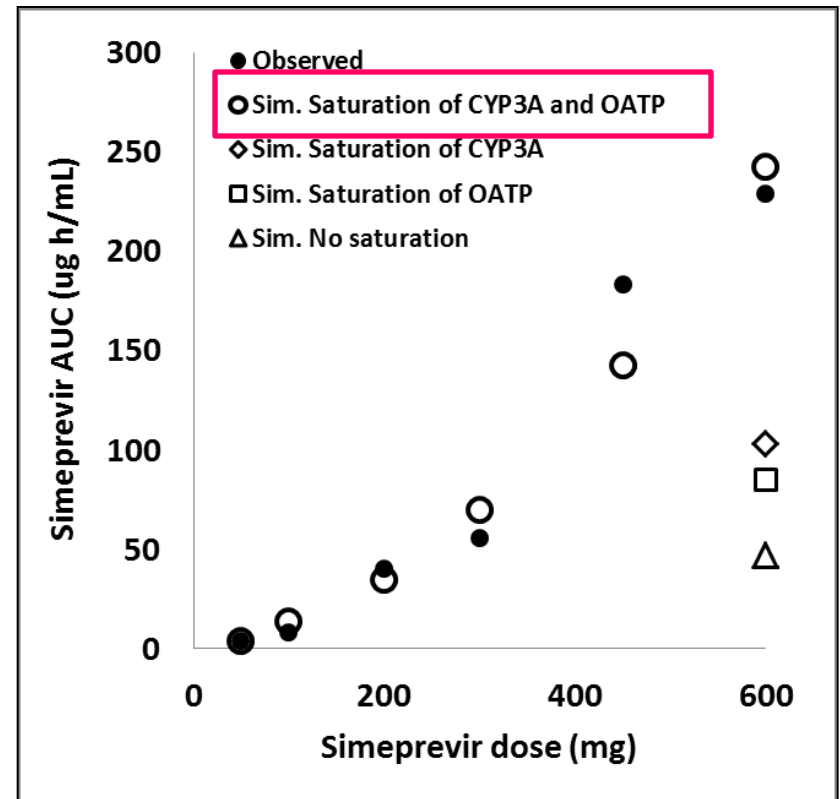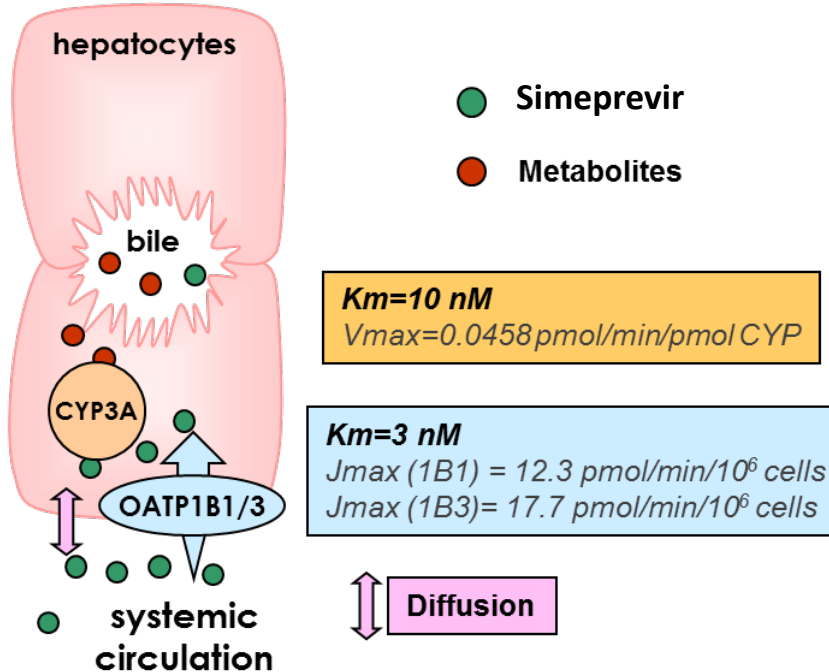
- Simeprevir demonstrates nonlinear PK (more than dose proportional change in exposure)

Source: Drugs@FDA (NDA 205123 Clin Pharm Review)

Simeprevir (HCV)
OATP1B1/3 and CYP3A4 Saturation →
Nonlinearity

Permeability-limited liver model

hepatocytes

● Simeprevir
● Metabolites

bile

CYP3A

OATP1B1/3

systemic circulation

Diffusion

Km=10 nM
Vmax=0.0458 pmol/min/pmol CYP

Km=3 nM
Jmax (1B1) = 12.3 pmol/min/10⁶ cells
Jmax (1B3)= 17.7 pmol/min/10⁶ cells

● Observed
○ Sim. Saturation of CYP3A and OATP
◇ Sim. Saturation of CYP3A
□ Sim. Saturation of OATP
△ Sim. No saturation

Simeprevir AUC (ug h/mL) vs Simeprevir dose (mg)

A Physiology-Based PK (PBPK) model was developed and verified using complex DDI data with different types of interacting drugs. The model suggested that the nonlinearity is captured only when both OATP1B1/3 and CYP3A4 saturation are incorporated → **unstudied scenarios**
(Drugs@FDA – NDA 205123 review; Chinn, Pan, Zhao, *et. al*.)   **Courtesy: P. Zhao**

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Summary

Transporter-based DDIs are being increasingly evaluated during drug development.
--One of the factors contributing to variability in PK, PD, efficacy, and safety

In vitro transporter studies increase our ability to predict occurrence of *in vivo* DDIs and aid in development of clinical DDI strategies.
 -- Best practice for *in vitro* transport assays is needed

Decision criteria proposed are being used to predict DDI potential and need to be further evaluated and refined when more data are available.
 -- Need to consider other pathways when using decision trees or use multiple trees for the same pair of substrate and inhibitor
 -- Basic →Mechanistic model

Transporter research is still rapidly evolving. Emerging transporters with clinical importance may need to be considered.
--Transporter's role in toxicity or efficacy needs to be understood (e.g., OCT1)

Acknowledgements

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  - Shiew-Mei Huang
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    - Xinning Yang, Vincent (Peng) Duan, Ping Zhao, Yuzhuo Pan, Vikram Arya, Leslie Chinn, Sue-Chih Lee, Sheetal Agarwal, Donna Volpe, Jaya Vaidyanathan, Ying Fan, Manuela Vieira
  - **Office of Clinical Pharmacology Review Staff and Fellows**

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  - International Transporter Consortium (ITC)
  - EMA and PMDA
  - Innovation & Quality Consortium (IQC)
  - Academia Collaborators
    - U of California, San Francisco
    - U of Maryland
    - U of Washington

Thank You!

Lei Zhang

leik.zhang@fda.hhs.gov

FDA Drug Development and Drug Interaction Website:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm